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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/817,328	DING ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/9/2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *2-5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 6-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/10/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-17 are pending.

Election/Restrictions

Applicant's election with traverse of Group II, claims 1 and 6-17, wherein X^1or X^2 is nitrogen and the other is carbon, namely pyrimidine compound, composition and method of use, along with election of species of Example 6, in paper dated 11/09/2005, is acknowledged. Claims 1 and 6-17 will be examined to the extent they embrace the elected subject matter. Claims 2-5 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i). The traversal is on the ground(s) that it is not serious burden search and the instant invention has common structural element.

Applicants' traversal of the restriction requirement is not persuasive for reasons of record. As for the traversal, the following apply.

First of all, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(A) The inventions must be independent (see MPEP § 802.01, § 806.04, § 808.01) or distinct as claimed (see MPEP § 806.05 - § 806.05(i)); and

(B) There must be a serious burden on the examiner if restriction is required (see MPEP § 803.02, § 806.04(a) - § 806.04(i), § 808.01(a), and § 808.02).

Both these criteria are to be met with.

1. Contrary to applicants' urging, both these criteria, distinct and independent Invention and search burden as basis for the restriction requirement, were clearly presented in the previous office action. To summarize, principles of classification dictate that ring structures with different ring sizes and having different numbers of heteroatoms to be classified in different classes. Such classification, as noted in the previous office action, stems from the fact that the ring structures have different properties, different reactivities and different effects on the substituents. They are made and used differently. In the instant case, the there are several hetero rings embraced in the instant claims such as 1,3,5-triazine, isomeric pyrmidines, pyridine, and various heterocyclic rings recited positively for R^3. Applicants have not asserted that the core groups are all equivalent. In which case, prior art, which anticipates instant elected invention, may then render the non-elected inventions as obvious variant and can thus be applied.

2. Applicants' argument that there is no serious search burden to examine all said groups is totally incorrect. First of all, as noted above, they are directed to structurally dissimilar compounds that lack common core. Consequently, the groups have different classifications and require separate prior art searches. It is mandatory for the examiner to search all classes and subclasses. Contrary to applicants' urging it would not be possible with the limited fixed time available for the examiner to examine each case with thorough search. Searching all possible classes and subclasses

embraced by the generic and specifically recited core would of serious search burden. The class 544 includes six membered heterocyclic rings with two or more hetero atoms and the east database has 12885 patents. Similarly the composition and method of use class 514 has 271213. To suggest that examiner can search the classes by themselves, lacks understanding of the time it takes to search each and every patent for the various limitations embedded in the claims. In order to further reduce burden USPTO classification provides distinct subclasses related each distinct heterocyclic core. Even with such subclasses variation in substituents patterns results more than one subclass to search and thus leads to serious search burden if all heterocyclic cores are to be searched.

Applicants have argued that the above two criteria set forth in MPEP as noted above is not applicable to instant case as they involve Markush group. The passage MPEEP 803.02 clearly states as quoted by the applicants that even if the inventions are distinct and independent there should not be any serious search burden. As noted above searching all the cores heterocyclic groups would be serious search burden.

To elaborate further, examiner has to search a commercial database-STN-CAPLUS for structure search and also have to search patent literature database- East and or West. These two are mandatory. In addition, it is essential to search NPL database.

In the instant case, the structure search in CAPLUS would involve searching triazine, isomeric pyrimidines, pyridine core compounds. Such a search would never

run to completion as it would exceed one million or more compounds upper limit set forth for in Registry file.

Without completion of the search it is not possible to perform further search and examine.

This is clearly the case as shown in the Search Notes I. Even if one limits to the elected core isomeric pyrimidine core, the search would not run to completion as there are more than million hits. This is shown in Search Note II. After several such searches, examiner had relied on the core of elected genus and searched a subgenus wherein L is a bond. See search note III. Applicants are urged to review these search notes to understand the extent of the search burden.

In addition, to this search, examiner has to classified and searched all controlling cores based on the elected subject matter to cover the full scope of the elected claims in East (or West). This includes plural pyridine cores, plural thiophene cores, plural furan cores and plural pyyrole cores. To illustrate the extent of search burdern, if one were to search class 544, which includes six membered heterocyclic rings with two or more hetero atoms, embraced by triazine and pyrimidine, the east database has 12885 patents. This would be a serious burden to search. In the instant case, in addition one has to search class 546 for pyridine, 514 for composition and method of use.

In order to further reduce burden USPTO classification provides distinct subclasses related each distinct heterocyclic core. Even with such subclasses variation in substituents patterns results more than one subclass to search and thus leads to serious search burden if all heterocyclic cores are to be searched. This is shown in the

Search note where all such classes/subclasses related to the elected subject matter is searched and reviewed for applying prior art. It should be self evident that the number patents to searched is too many to justify that the search is indeed a serious burden in the instant case.

3. Examiner also noted in the previous office action "Should applicant traverse on the ground that the core species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention". Applicants have not asserted that the two groups are not distinct. Applicants have not submitted evidence or identified such evidence now of record showing the core group to be obvious variants or clearly admitted on the record that all core groups embraced in the instant inventions are equivalent. In which case examiner needed not search all cores. A prior art which anticipates any one of the groups embraced by a specific core (i.e. choices of I, II,III) may then render rest of the core groups as obvious variant. In other words, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

In want of such assertion or evidence, searching the all the three Groups would be serious search burden.

Applicants have not addressed the two criteria, distinct and independent inventions and search burden, set forth for restriction requirements.

As for rest of applicants' argument, 37 C.F.R §1.141, as quoted by the applicants, states "an applicant may not claim two or more independent and distinct inventions in a single application." As noted above, there are three independent and distinct inventions in the instant case. Hence, the above is not to the point. Secondly, contrary to applicants' assertion, there is no genus-species relationship. The three groups are distinct genus bundled as one in the application. In fact there is no species claim. As long as the three inventions are distinct and independent and that the search imposes serious burden, the restriction as set forth is proper.

Furthermore, applicants' argument that the three distinct and independent invention does not embrace the total scope of claim 1 is incorrect. Three Groups include claim 1 and as such cover the full scope of claim 1. Hence, there inventions bundled together would have the same scope for each of the inventions.

Applicants also have argued that invoking In re Weber and In re Harnish that the restriction requirement is improper. Again this argument is not persuasive and the case laws cited are not the point. Careful analysis of the case laws will show that there is condition clause that unity of invention should be considered. To quote MPEP 803 'Since the decisions In re Weber, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and In re Haas, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. In re Harnish, 631 F.2d 716, 206 USPQ 300 (CCPA

1980); and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility.

First of all, the instant application is not 371 of PCT application entering national stage. It is a US application and that the only criteria for restriction is as stated above, whether the inventions are independent and distinct and whether the search is a serious search burden. As noted above, instant inventions fail to meet both these conditions.

Secondly, applicants have not shown what portion of the core share a substantial structural feature disclosed as being essential to that utility.

Finally, the references provided by the applicants in IDS as well as those now applied clearly shows structurally related pyrimidine compounds of instant claims have different utility, which would negate the common utility requirement & sharing the substantial structural feature.

Based on the foregoing reasons, the requirement is still deemed proper and is therefore made FINAL.

Claims 1 and 6-17 are now under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 6-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention. Following reasons apply. Any claim not specifically rejected is rejected as being dependent on a rejected claim.

1. Recitation of " and pharmaceutically acceptable salts, hydrates, solvates, isomers and prodrugs thereof" in claim 1, renders this claim indefinite as it is not clear whether the claim is compound claim or composition claim with above said limitations. Note Markush recitation should be in alternate form and in singular.

2. Recitation of "prodrug thereof" in claim 1 and "prodrug derivative" in claim 17 renders these claims and its dependent claims 6-16 indefinite. Prodrugs in general and as noted in specification, are compounds, which undergo in vivo hydrolysis to parent active drugs. In that sense recitation of prodrug is acceptable. However, the definition of various variable groups include such groups, namely esters, amides, alkoxycarbonyl etc. and therefore it is not clear what is the difference between these variable groups and the prodrug groups. There is clear-cut ambiguity as to what is to be considered as prodrug and what is not. Applicants should note that if the variable groups are prodrug, which are in general inactive but becomes active upon in vivo transformation, then the compound bearing the variable group would be deemed as inactive which is not what the claim recites.

Furthermore, the issue on second paragraph is whether the structures of the claimed compounds are clearly defined. Applicants' "prodrugs" are molecules whose structure lie outside the subject matter of formula (I), but upon metabolism in the body are converted to active compounds falling within the structural scope of formula (I). The claim describes the function intended but provides no specific structural guidance to

what constitutes a "prodrug". Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claim 1. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise.

3. Depiction of R^2 as a floating group renders claim 1 and claim 6-17 indefinite as it is not clear how this group could have varible point of attachment. Note when X^1 and X^2 are –N= or –CR^4=, there is only one position available for R^2.

3. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the reagents essential for the reaction are omitted.

4. Claim 17 is also indefinite as it is not clear how the second choice is implemented. Note "or" before second choice. How could one convert a compound to salt without making the compound?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 6-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrug of the claimed compounds. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry - to use the invention.

"The factors to be considered in making an enablement rejection have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", In re Rainer, 146 USPQ 218 (1965); In re Colianni, 195 USPQ 150, Ex parte Formal, 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, and produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism 'de novo, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Thus, determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

The direction concerning the prodrug is found in page 6 the passage 0034, page 15, a passage 0062. There is no working example of a prodrug of a compound the formula (I). The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) The state of the prodrug art is summarized by Wolff (Medicinal Chemistry). The table on the left side of page 976 outlines the research program to be undertaken to. find a prodrug. The second

paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modem Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. It is well established that "the scope of enablement varies inversely degree of unpredictability of the factors involved", 'and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim I as well as the presently unknown list potential prodrug derivatives embraced by the word "prodrug".

Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright,

999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Claims 1 and 6-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making pharmaceutically acceptable salts does not reasonably provide enablement for making solvate or hydrate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The following apply.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. **The nature of the invention and the state of the prior art:**

The invention is drawn to compound of formula I, or a pharmaceutically acceptable salt solvate or hydrate thereof. Specification is not adequately enabled as to how to make hydrate of compounds of formula (I) Specification has no example of hydrate of the instant compounds. Specification on page 6 and 15 recites solvate or hydrate thereof but there is no enabling of such compounds.

The compound of formula I embrace pyrimidine compounds substituted with variable groups R^1, R^2, R^3 and R^4.

Even a cursory calculation of the number of compounds embraced in the instant formula (I) based on the generic definition of alkyl., aryl heteroaryl, heterocyclyl, substituted aryl, heteroaryl, arylalkyloxy, arylalkylthio etc would result in hundreds of thousands of compounds. This is of course not the accurate number and the true number of compounds would far exceed this number of compounds. Thus the genus embraced in the claim 1 is too large and there is no teaching of any hydrate or solvate of this large genus.

Search in the pertinent art, including water as solvent resulted in a pertinent reference, which is indicative of unpredictability of hydrate formation in general. The state of the art is that is not predictable whether solvates or hydrates will form or what their composition will be. In the language of the physical chemist, a hydrate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. Compared with polymorphs, there is an additional degree

of freedom to hydrates, which means a different solvent or even the moisture of the air that might change the stabile region of the hydrate. In the instant case of hydrate a similar reasoning therefore apply. Water is a solvent and hence it is held that a pertinent detail of West, which relates to solvates, is also applicable to hydrate

In addition, an additional search resulted in Vippagunta et al., Advanced Drug Delivery Reviews 48: 3-26, 2001, which clearly states that formation of hydrates in unpredictable. See entire document especially page 18, right column section 3.4. Note Vippagunta et al., states "Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for series of related compounds".

2. **The predictability or lack thereof in the art:**

Hence, the solvate and hydrate as applied to the above-mentioned compounds claimed by the applicant are not art-recognized compounds and hence there should be adequate enabling disclosure in the specification with working example(s).

3. **The amount of direction or guidance present:**

Examples illustrated in the experimental section are limited to making the compounds not related to solvates and hydrates. There is no example of a solvate or hydrate of instant compound. One hundred and twenty-six compounds were shown in the examples of the specification each of which has come in contact with water and other solvent but there is no showing that instant compounds formed solvates or hydrates. Hence it is clear that merely bring the compound with solvent or water does

not result in solvate or hydrate and additional direction or guidance is needed to make them Specication has no such direction or guidance.

4. **The presence or absence of working examples:**

There is no working example of any solvate or hydrate formed. The claims are drawn to hydrate, yet the numerous examples presented all failed to produce a solvate or hydrate or even hydrate. These cannot be simply willed into existence. As was stated in Morton International Inc. v. Cardinal Chemical Co., 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ...' no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that hydrates of these compounds actually exists; if they did, they would have formed. Hence, there should be showing supporting that solvates and hydrates of these compounds exist and therefore can be made.

5. **The breadth of the claims & the quantity of experimentation needed:**

Specication has no support, as noted above, for compounds generically embraced in the claim 1 would lead to desired solvate and hydrate of the compound of formula I. As noted above, the genus embraces over million compounds and hence the breadth of the claim is broad. The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of

experimentation, there is no guarantee that one would get the product of desired hydrate of compound of formula I embraced in the instant claims in view of the pertinent reference teachings.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Claim 17 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds wherein X^1 and or X^2 is N or CH, C-alkyl and R^2 is H or alkyl, does not reasonably provide enablement for R^2 is halo or for compounds wherein R^3 is substituted reactive functional groups as recited for compound of claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In evaluating the enablement question, following factors are considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or

absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. The nature of the invention and the state of the prior art:

The invention is drawn to compound of formula shown in claim 1 wherein the X^1 and or X^2 is N or CH, C-alkyl and R^2 is H, halo, amino, alkyl and alkoxy as well as various reactive functional substituents in the definition of R^3. Claim 17 thus permits halogen substituents which would also behave as Q group recited in claim 17 and undergo reaction with compound of formula 3 and 4. The same is true for various reactive groups of R^3 which can also undergo nucleophilic substitution with compound of formula 5 and 6. Specification is not adequately enabled as to how to make compounds of formula shown in claim 1 wherein the above said groups are present in the compound of formula I , which are also susceptible to the process.

Specification offers no teachings or suggestion as to how to perform the said reaction and make such compounds in presence of these reactive groups.

2. The predictability or lack thereof in the art:

The process of arylation and or nucleophilc as applied to the above-mentioned compounds claimed by the applicant is not an art-recognized process and hence there should be adequate enabling disclosure in the specification with working example(s) to make these claimed compounds.

4. The amount of direction or guidance present:

Examples illustrated in the experimental section or written description offer no guidance or teachings as to how make these compounds when reactive substituents or chemically incompatible substituents are present in the starting material.

5. The presence or absence of working examples:

Although examples on pages 21-44 show enablement for number of compounds, they are limited to compounds with no reactive functionality. There are no representative examples showing the viability of the process for the reactive halo or other groups embraced in the instant claim.

6. The breadth of the claims:

Specification has no support, as noted above, for all compounds generically embraced in the claim language would lead to desired compound of formula I with said reactive groups and there is also no valid chemical reasoning for one trained in the art to expect that all these functional groups would be inert toward the reaction to make such halo, amino or hydroxy of R^2 and other reactive functional groups of R^3 compounds.

7. The quantity of experimentation needed:

The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired structure, namely compound of formula shown in claim 1 in view of the general reactive of above said functional groups. Thus, factors such as "sufficient working examples", the "level of skill in the art and

predictability, etc. have been demonstrated to be sufficiently lacking in the case for the instant claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-16 are rejected under U.S.C. 112, first paragraph, because the specification while being enabling for treating breast cancer, does not reasonably provide enablement for treating any or all tumoral disease generically embraced in these claims. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims.

The instant method of use claims 12-16 are drawn to "treatment of warm-blooded animals suffering from tumoral disease" by inhibiting receptor tyrosine kinases in general. Instant claims, as recited, are reach through claims. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the inhibition of tyrosine kinase by the instant compounds, claims 12-16 are reach through treating any or all tumoral diseases in general and thereby they lack adequate written description and enabling disclosure in the specification.

More specifically, in the instant case, based on the mode of action of instant compounds as inhibitor of tyrosine kinase, it is claimed that treating any or all tumoral

diseases in general. The scope of the claims includes any or all tumoral diseases due to receptor tyrosine kinase inhibition including those yet to be discovered as due said mode of action for which there is no enabling disclosure. In addition, the scope of treatment of tumoral diseases would include treatment of various cancers including group consisting of lung cancer, bone cancer, pancreatic cancer, skin cancer. cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region. stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers, which is not adequately enabled solely based on the activity of the compounds provided in the specification. The instant compounds are disclosed to have receptor tyrosine kinase inhibitory activity and it is recited that the instant compounds are therefore useful in treating any or all diseases stated above for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as tyrosine kinase inhibitor

that would be useful for all sorts of tumoral diseases. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such as psoriasis, lung cancer, brain cancer, pancreatic cancer, colon cancer etc. are very difficult to treat and despite the fact that there are many anticancer drugs.

The scope of the claims involves millions of compounds of claim 1 as well as the thousand of diseases embraced by the terms tumoral diseases.

Tumoral disease would include benign tumors, malignant tumors, polyps, lumps, lesions, other pre-cancerous conditions, psoriasis, leukemia, the hyper proliferation of the gastric epithelium caused by the Helicobacter pylori infection of ulcers.

Cancer is just an umbrella term. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless.

No compound has ever been found to treat tumoral diseases of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. Note substantiation of

utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Mass, R. D., Int. J. Radiation Oncology Bio. Phys.Vol. 58(3): 932-940, 2004 and Fabbro et al. Pharmacology & therapeutics 93, 79-98, 2002.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating tumoral diseases that require receptor tyrosine kinase inhibitory activity.

2) The state of the prior art: Recent publications expressed that the receptor tyrosine kinase inhibition effects are unpredictable and are still exploratory. See Mass et al. and Fabbro et al., cited above especially the concluding paragraph.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all tumors by the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all tumoral diseases and the state of the art is that the effects of tyrosine kinase inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace treatment of any or all tumoral diseases with large genus of compounds.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical

nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 , 6-8 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Boykin et al., US 5,686,456.

Boykin et al. teaches several 2,4-substitutedpyrimidine compounds for treating Pneumocystis carnii which includes instant compounds. See column 2, formula 1 and

note the definition of various variable groups. Especially note when R_4 is hydrogen or alkyl, R_5 is hydrogen, alkyl, halogen or alkoxy, with the given definition of other substituents, compounds taught by Boykin et al. include instant compounds. See entire document. See column 8-21 for various compounds which include instant compounds.

Claims 1 , 6-8 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Carling et al., US 5,763,448.

Carling et al. teaches several pyrimidine compounds for treating schizophrenia which include instant compounds. See column 1, formula 1 and note the definition of A, Q, R^1 and R^2 groups. Especially note the definition of A, Q, R^1 and R^2 groups clearly overlaps with the definition of instant R^1, L-R^3, R^2 and R^4 groups and compounds taught by Carling et al. therefore include instant compounds. See column 2-8 for further details of the invention. See column 9-11 for species of compounds which include instant compounds.

Claims 1, 6, 9, 10 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Cuccia et al., US 6,281,219.

Cuccia et al. teaches several pyrimidine compounds useful as insecticides which include instant compounds. See column 1, formula 1 and note the definition of various variable groups. Especially note the definition of phenyl-X_1, phenyl-X_2 and R^1 groups clearly overlaps with the definition of instant R^1, L-R^3, R^2 and R^4 groups and compounds taught by Cuccia et al. therefore include instant compounds. See column 2-17 for further details of the invention including the process of making which includes

instant process. See column 18-23 for species of compounds which include instant compounds.

Claims 1, 6, 9, 10 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Wood et al., US 6,306,866.

Wood et al. teaches several pyrimidine compounds useful as insecticides which include instant compounds. See column 3-4, formula 1A, IB and IB1 and note the definition of A-X, B, and R^1 groups. Especially note the definition of A-X, B, and R^1 groups clearly overlaps with the definition of instant the definition of R^1, L-R^3, R^2 and R^4 groups and compounds taught by Wood et al. therefore include instant compounds. See entire document for further details of the invention. See column 6-14, especially Table I-III, for species of compounds which include instant compounds.

Claims 1, 6, 9, 10 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Scheiblich et al., US 6,313,072.

Scheilblich et al. teaches several pyrimidine compounds useful as herbicides which include instant compounds. See column 3-4, formula 1A, IB and IB1 and note the definition of A-X, B, and R^1 groups. Especially note the definition of A-X, B- R^3, R^1 and R^2 groups clearly overlaps with the definition of instant the definition of R^1, L-R^3, R^2 and R^4 groups and compounds taught by Scheilblich et al. therefore include instant compounds. See column 2-11 for further details of the invention and process of making. See column 12-13, especially Table, for species of compounds which include instant compounds.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6-8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boykin et al., US 5,686,456.

Teachings of Boykin et al. as discussed in the above 102 rejection is incorporated herein. As noted above, Boykin et al. teaches several 2,4-

substitutedpyrimidine compounds for treating Pneumocystis carnii which includes instant compounds. See column 2, formula 1 and note the definition of various variable groups. Especially note when R_4 is hydrogen or alkyl, R_5 is hydrogen, alkyl, halogen or alkoxy, with the given definition of other substituents, compounds taught by Boykin et al. include instant compounds. See entire document. See column 8-21 for various compounds which include instant compounds.

Boykin et al. differs in exemplifying not all compounds generically embraced in the compound of formula I.

However, Boykin et al. teaches equivalency of those compounds taught in column 8-21 with those generically recited in column 2

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Boykin et al and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above.

Claims 1, 6-8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carling et al., US 5,763,448.

Teachings of Carling et al. as discussed in the above 102 rejection is incorporated herein. Carling et al. teaches several pyrimidine compounds for treating schizophrenia which include instant compounds. See column 1, formula 1 and note the definition of A, Q, R^1 and R^2 groups. Especially note the definition of A, Q, R^1 and R^2 groups clearly overlaps with the definition of instant R^1, L-R^3, R^2 and R^4 groups and compounds taught by Carling et al. therefore include instant compounds. See column 2-

8 for further details of the invention. See column 9-11 for species of compounds which include instant compounds.

Carling et al. differs form the instant claims in not exemplifying all compounds generically embraced in the formula I shown in column 1.

However, Carling et al. teaches equivalency of those compounds taught in examples 1-5 with those generically recited for compound of formula I in column 1.

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Carling et al and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above.

Claims 1, 6, 9, 10 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cuccia et al., US 6,281,219.

Teachings of Cuccia et al. as discussed in the above 102 rejection is incorporated herein. Cuccia et al. teaches several pyrimidine compounds useful as insecticides which include instant compounds. See column 1, formula 1 and note the definition of various variable groups. Especially note the definition of phenyl-X_1, phenyl-X_2 and R^1 groups clearly overlaps with the definition of instant R^1, L-R^3, R^2 and R^4 groups and compounds taught by Cuccia et al. therefore include instant compounds. See column 2-17 for further details of the invention including the process of making which includes instant process. See column 18-23 for species of compounds which include instant compounds.

Cuccia et al. differs form the instant claims in not exemplifying all compounds generically embraced in the formula I shown in column 1.

However, Cuccia et al. teaches equivalency of those compounds taught in examples 1-39 with those generically recited for compound of formula I in column 1.

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Cuccia et al and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above.

Claims 1, 6, 9, 10 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wood et al., US 6306,866.

Teachings of Wood et al. as discussed in the above 102 rejection is incorporated herein. Wood et al. teaches several pyrimidine compounds useful as insecticides which include instant compounds. See column 3-4, formula 1A, IB and IB1 and note the definition of A-X, B, and R^1 groups. Especially note the definition of A-X, B, and R^1 groups clearly overlaps with the definition of instant the definition of R^1, L-R^3, R^2 and R^4 groups and compounds taught by Wood et al. therefore include instant compounds. See entire document for further details of the invention. See column 6-14, especially Table I-III, for species of compounds which include instant compounds.

Wood et al. differs form the instant claims in not exemplifying all compounds generically embraced in the formula IA, IB and IB1 shown in column 3-4.

However, Wood et al. teaches equivalency of those compounds taught in examples 1-5 with those generically recited for compound of formula I in column 3-4.

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Wood et al and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above.

Claims 1, 6-8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scheiblich et al., US 6,313,072.

Teachings of Scheilblich et al. as discussed in the above 102 rejection is incorporated herein.

Scheilblich et al. teaches several pyrimidine compounds useful as herbicides which include instant compounds. See column 3-4, formula 1A, IB and IB1 and note the definition of A-X, B, and R^1 groups. Especially note the definition of A-X, B- R^3, R^1 and R^2 groups clearly overlaps with the definition of instant the definition of R^1, L-R^3, R^2 and R^4 groups and compounds taught by Scheilblich et al. therefore include instant compounds. See column 2-11 for further details of the invention and process of making. See column 12-13, especially Table, for species of compounds which include instant compounds.

Scheilblich et al. differs form the instant claims in not exemplifying all compounds generically embraced in the formula I shown in column 1.

However, Scheilblich et al. teaches equivalency of those compounds taught in examples 1-18 with those generically recited for compound of formula I in column 1.

Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Scheilblich et al

and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outline above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 6-17 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 57-72 of copending Application No. 10/270,030. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter namely aryl substituted pyrimidines embraced in the instant claims are also embraced in the copending application 10/270,030.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571)

272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

1/21/2005